Figure 5. Mean Plasma Nelfinavir Concentration Versus Time Profile After Multiple Oral Doses of Nelfinavir 750 mg TID Both With and Without Half-Dose Rifabutin (150 mg Daily)

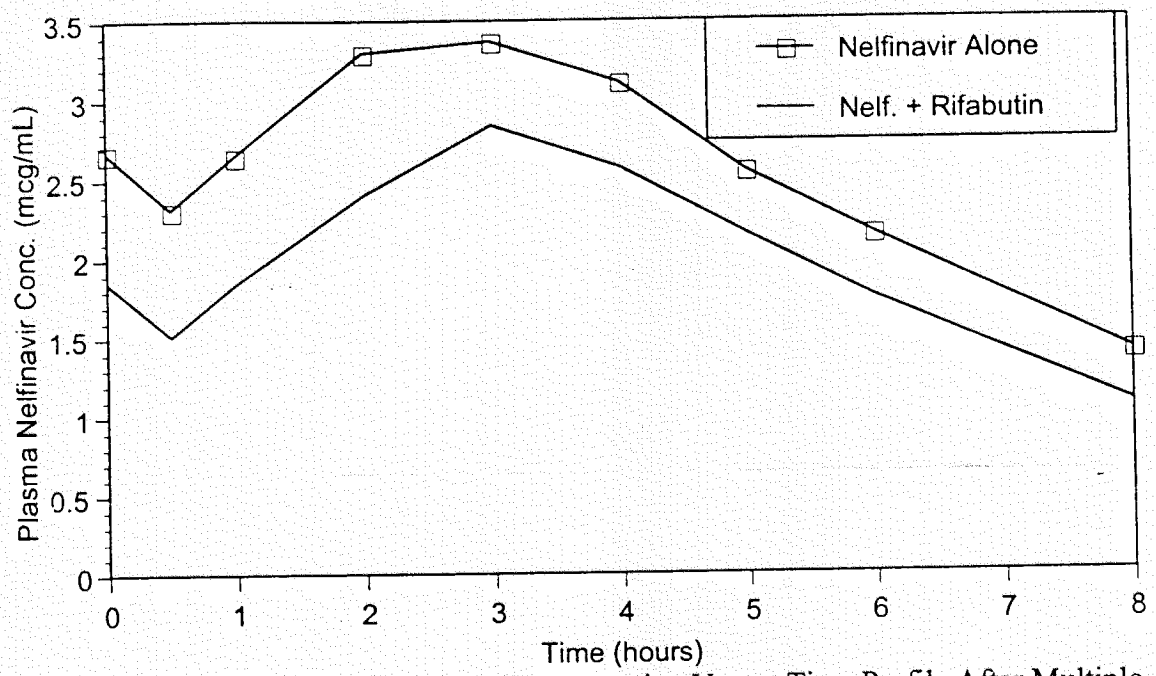

Figure 6. Mean Plasma AG1402 Concentration Versus Time Profile After Multiple Oral Doses of Nelfinavir 750 mg TID Both With and Without Half-Dose Rifabutin (150 mg Daily)

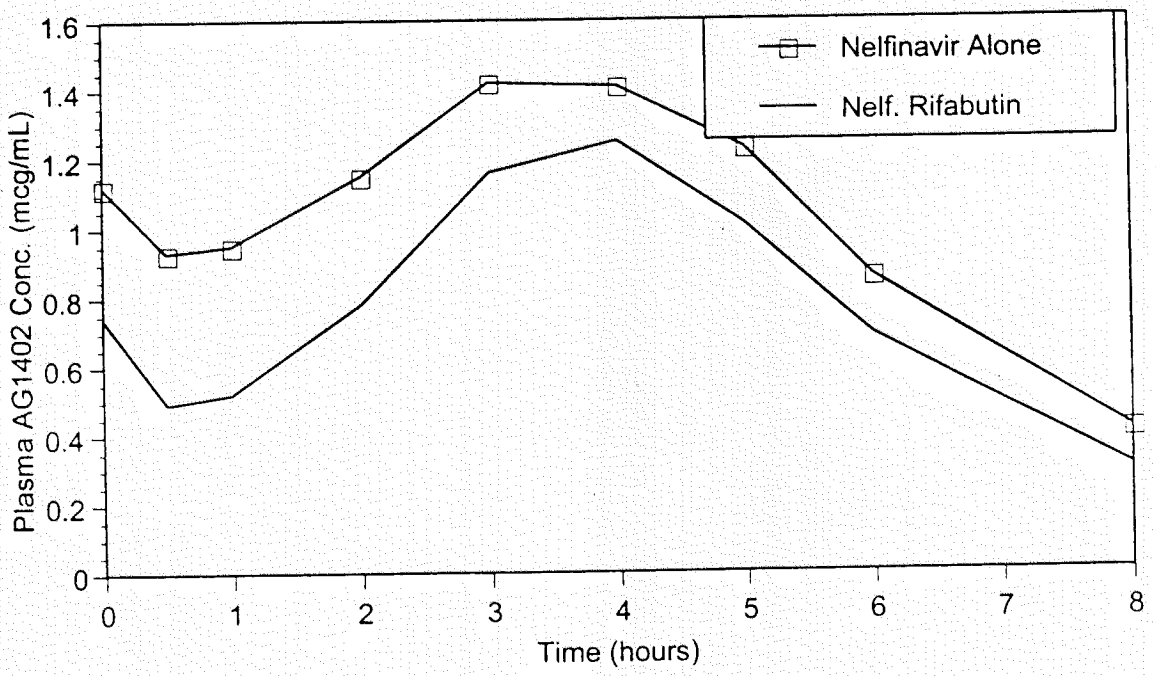

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Figure 7. Mean Plasma Rifabutin Concentration Versus Time Profile After Multiple Daily Oral Doses of Rifabutin (300 mg Alone, or 150 mg With Nelfinavir TID)

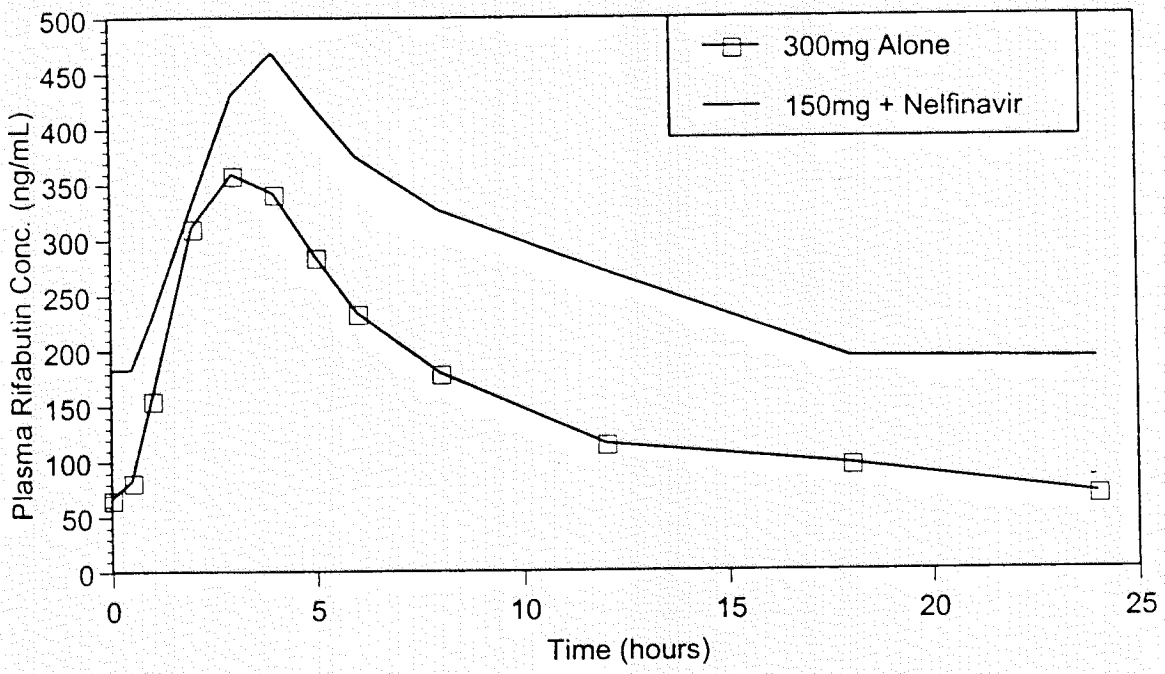

Figure 8. Mean Plasma Desacetylrifabutin Concentration Versus Time Profile After Multiple Daily Oral Doses of Rifabutin (300 mg Alone, or 150 mg With Nelfinavir TID)

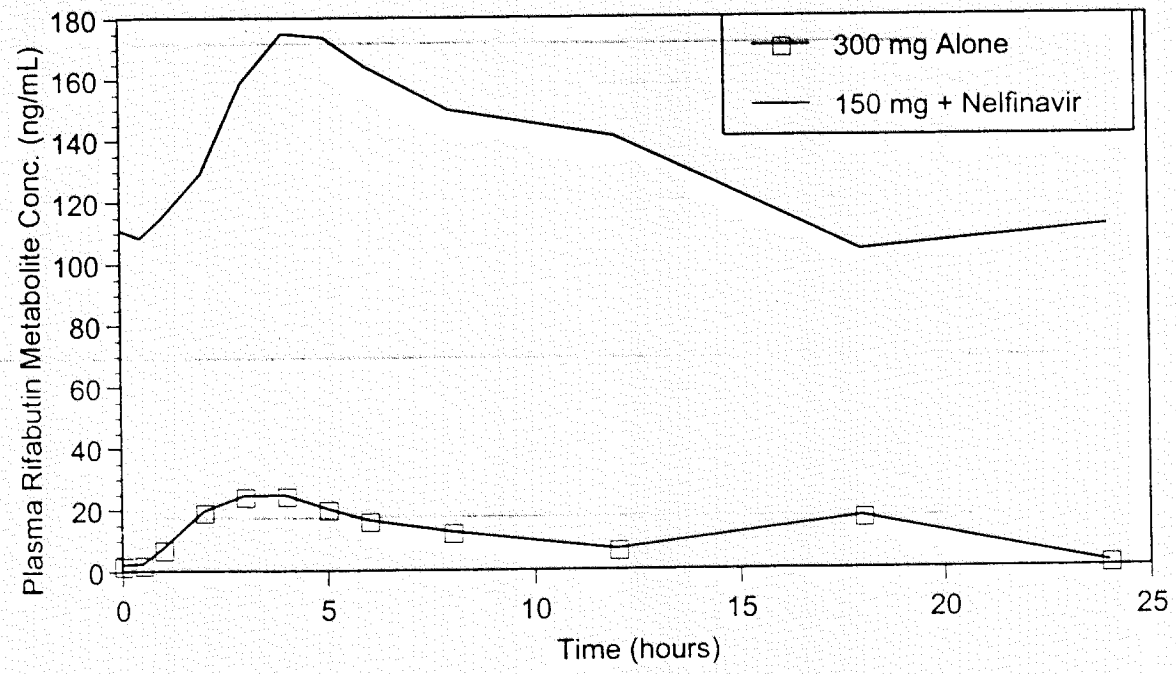

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Figure 9. Mean Plasma Nelfinavir Concentration Versus Time Profile After Multiple Oral Doses of Nelfinavir 1250 mg BID Both With and Without Half-Dose Rifabutin (150 mg Daily)

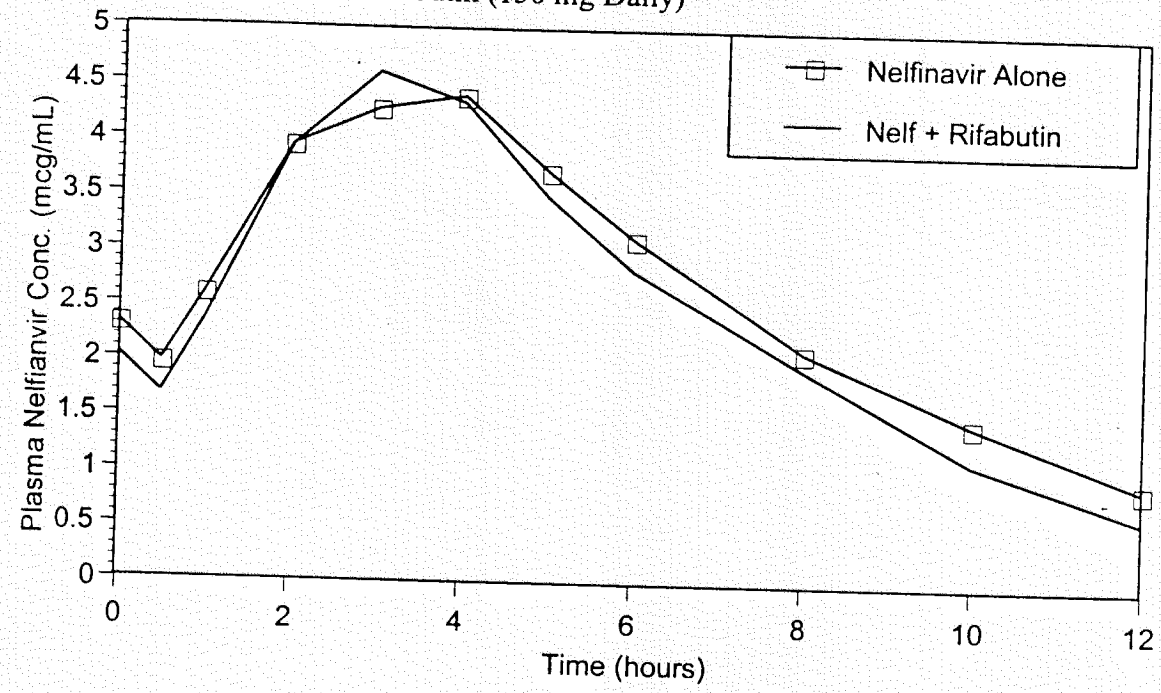

Figure 10. Mean Plasma AG1402 Concentration Versus Time Profile After Multiple Oral Doses of Nelfinavir 1250 mg BID Both With and Without Half-Dose Rifabutin (150 mg Daily)

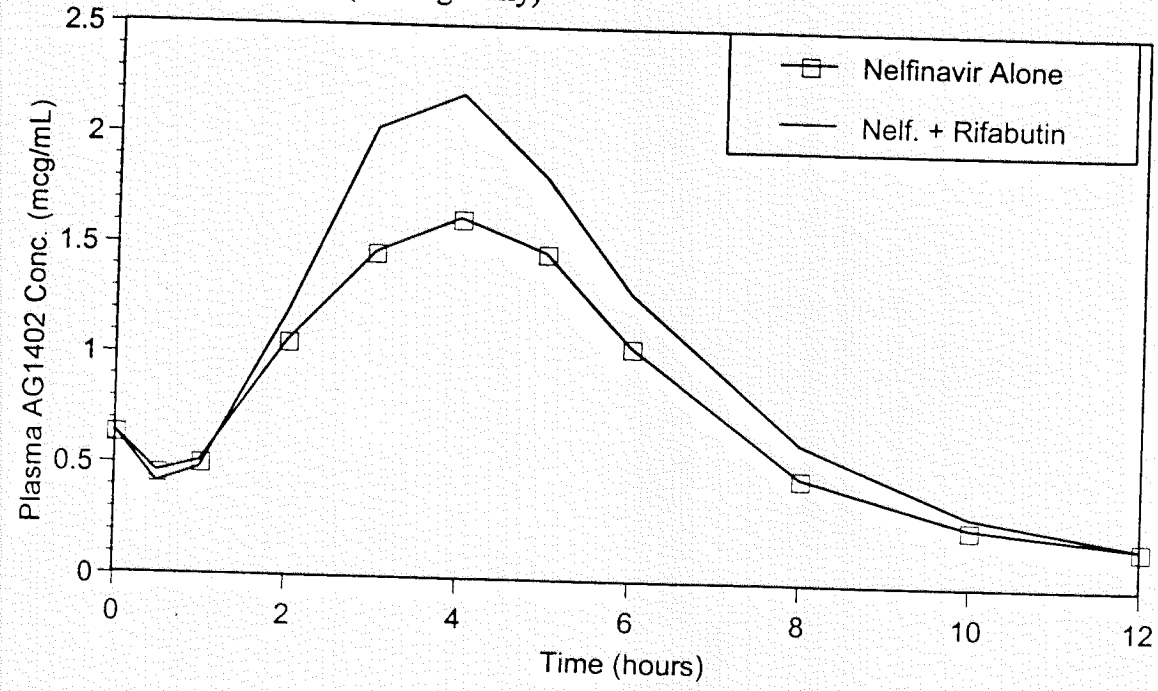

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Table 2. Mean (%CV) Nelfinavir Pharmacokinetic Parameters After Oral Multiple-Dose Administration of Nelfinavir (750 mg TID) With and Without Rifabutin (150 mg Daily)

	Nelfinavir Alone	*Nelf. + Rifabutin*	*Difference±SD*
AUC_τ (μg·hr/mL)	20.8 (28)	16.3 (31)	-22±15%
C_{max} (μg/mL)	3.61 (26)	3.01 (28)	-17±19%
T_{max}[4] (hr)	2 (1-5)	3 (2-4)	+50%
C_τ (μg/mL)	1.40 (38)	1.07 (45)	-24±29%
Cl/F (L/hr)	39.1 (30)	51.8 (40)	+32±24%

Table 3. Mean (%CV) AG1402 Pharmacokinetic Parameters After Oral Multiple-Dose Administration of Nelfinavir (750 mg TID) With and Without Rifabutin (150 mg Daily)

	Nelfinavir Alone	*Nelf. + Rifabutin*	*Difference±SD*
AUC_τ (μg·hr/mL)	8.36 (47)	6.37 (46)	-23±20%
C_{max} (μg/mL)	1.62 (42)	1.35 (40)	-17±25%
T_{max} (hr)	3 (0-5)	4 (3-5)	-33%
C_τ (μg/mL)	0.41 (57)	0.31 (60)	-24±30%
Cl/F (L/hr)	0.39 (42)	0.38 (37)	-3±16%

Table 4. Mean (%CV) Rifabutin Pharmacokinetic Parameters After Oral Multiple-Dose Administration of Rifabutin (300 mg Daily, alone and 150 mg Daily With Nelfinavir 750 mg TID)

	300 mg Alone	*Rifabutin + Nelf.*	*Difference±SD*
AUC_τ (μg·hr/mL)	3650 (17)	6681 (16)	+83±27%
C_{max} (μg/mL)	409 (14)	487 (15)	+19±15%
T_{max} (hr)	3 (1-5)	4 (2-5)	+33%
Cl/F (L/hr)	84.4 (17)	22.9 (15)	-73±4%

Table 5. Mean (%CV) Desacetylrifabutin Pharmacokinetic Parameters After Oral Multiple-Dose Administration of Rifabutin (300 mg Daily, alone and 150 mg Daily With Nelfinavir 750 mg TID)

	300 mg Alone	*Rifabutin + Nelf.*	*Difference±SD*
AUC_τ (μg·hr/mL)	240 (18)	3236 (22)	+1248±300%
C_{max} (μg/mL)	27.8 (20)	180 (17)	+547±114%
T_{max} (hr)	3 (1-5)	5 (4-6)	+67%

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[4] *Median (range)*

Table 6. Mean (%CV) Nelfinavir Pharmacokinetic Parameters After Oral Multiple-Dose Administration of Nelfinavir (1250 mg BID) With and Without Rifabutin (150 mg Daily)

	Nelfinavir Alone	*Nelf. + Rifabutin*	*Difference±SD*
AUC_τ (μg·hr/mL)	32.6 (47)	30.5 (37)	-6±23%
C_{max} (μg/mL)	4.78 (37)	4.76 (30)	---
T_{max}[5] (hr)	3 (2-4)	3 (2-4)	---
C_τ (μg/mL)	0.92 (93)	0.63 (66)	-32±86%
Cl/F (L/hr)	45.4 (45)	45.2 (29)	---

Table 7. Mean (%CV) AG1402 Pharmacokinetic Parameters After Oral Multiple-Dose Administration of Nelfinavir (1250 mg BID) With and Without Rifabutin (150 mg Daily)

	Nelfinavir Alone	*Nelf. + Rifabutin*	*Difference±SD*
AUC_τ (μg·hr/mL)	9.69 (48)	12.0 (53)	+24±24%
C_{max} (μg/mL)	1.80 (43)	2.25 (45)	
T_{max}[6] (hr)	4 (2-5)	4 (3-4)	---
C_τ (μg/mL)	0.19 (94)	0.19 (70)	---

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[5] *Median (range)*
[6] *Median (range)*

An investigation of the potential pharmacokinetic interaction between Nevirapine (VIRAMUNE) and nelfinavir (VIRACEPT) and the efficacy of this combination therapy in HIV-1 infected adults treated with stavudine [d4T] (ZERIT)

Study No. BI1100.1224 **Volumes** 74.5 – 74.8 (submitted to IND

Clinical Dates 5/15/97 – 1/20/98

Analytical Facility Nelfinavir

Nevirapine:

Analytical Dates Nelfinavir: 8/22/97 – 4/28/97

Nevirapine: 9/18/97 – 12/11/97

Objectives To assess the effect of concomitant nevirapine on the pharmacokinetics of nelfinavir.

Formulations

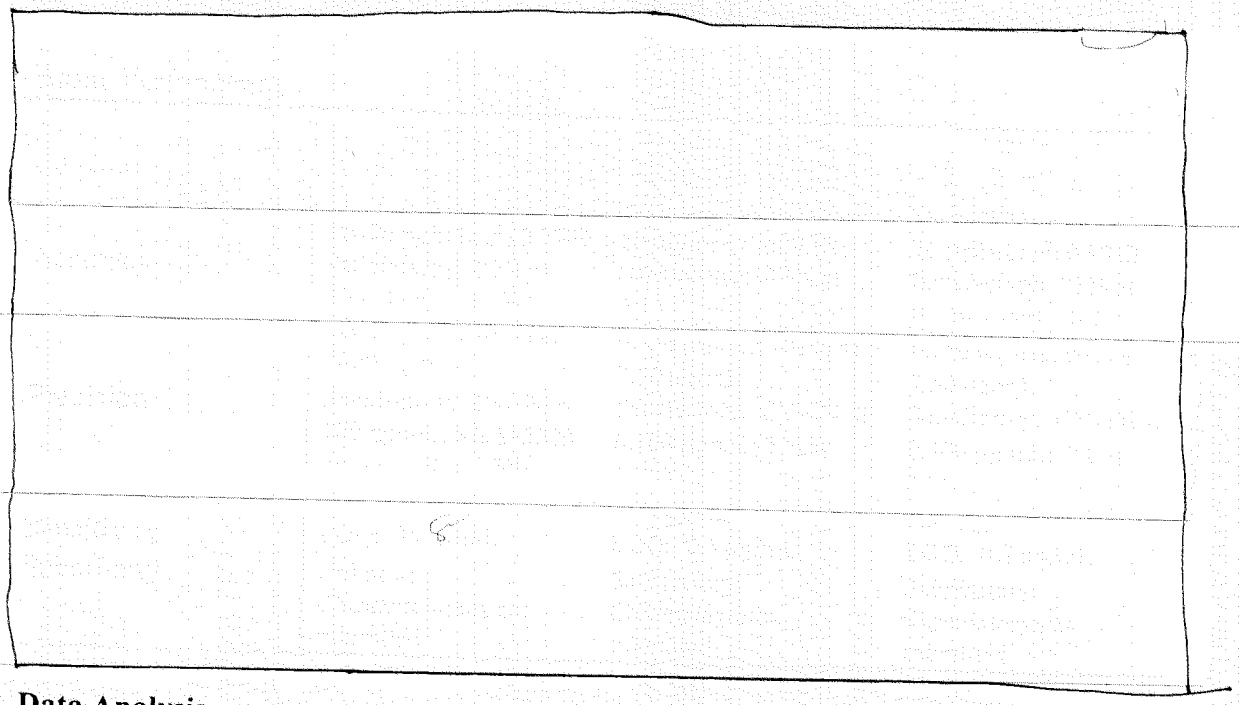
nelfinavir 250 mg tablets
stavudine 40 mg capsules
nevirapine 200 mg tablets

Study Design A total of 25 HIV-infected adult males and females were included in this open-label, multiple-dose, 1 sequence, add-on study. All subjects received nelfinavir 750 mg TID and stavudine 40 mg BID on study days 0 – 7. On days 8 – 21, nevirapine 200 mg daily was added. On days 22-36, the nevirapine dose was increased to 200 mg BID (this dose escalation strategy has been shown to decrease the incidence of nevirapine-induced rash). Subjects were confined overnight the evening before until after the completion of the pharmacokinetic sampling and abstained from the consumption of tobacco, alcohol and xanthine containing foods and beverages on pharmacokinetic evaluation days (pharmacokinetic evaluation days described below).

Sampling

Blood samples were obtained for plasma nelfinavir and AG1402 determinations just prior to (zero hour), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8 hours after study drug administration on Days 7 and 36. In addition, 10 and 12 hour samples were collected on Day 36. On Day 36, samples were collected for nevirapine assessments 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours after study drug administration.

Assay methods were used for plasma nevirapine, nelfinavir and AG1402 determinations



Data Analysis

Pharmacokinetic: $C_{max,ss}$, $C_{min,ss}$, $T_{max,ss}$, $AUC_{0-\tau,ss}$ and Cl/F

Statistical: The sponsor provided descriptive statistics for all pharmacokinetic parameters

Results A total of 22 subjects completed the study. Subjects 9704, 9707 and 9708 discontinued due to adverse events. The mean plasma concentration versus time profile for nelfinavir is presented in Figure 11. The sponsor did not provide mean concentration versus time data for either nevirapine or AG1402. Nevirapine and nelfinavir pharmacokinetic parameters are presented Tables 8 and 9. The sponsor did not provide parameter estimates for AG1402. Although the trial did not include a comparison arm for nevirapine, stavudine and lamivudine alone (without nelfinavir), parameter estimates obtained in the treatment arm were not materially different than those observed in another similarly designed study (BI1100.1203).

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Figure 11. Mean Nelfinavir Plasma Concentration versus Time Profile After Oral Administration of Nelfinavir 750 mg TID/Stavudine 40 mg BID Both With and Without Nevirapine 200 mg BID

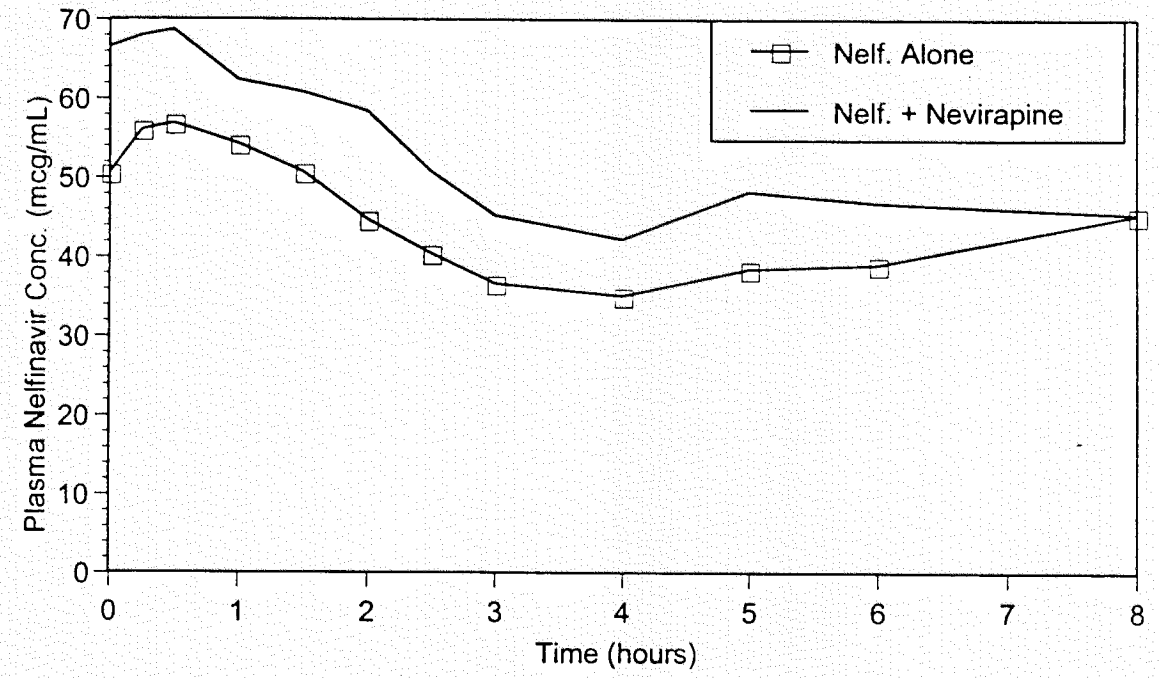

Table 8. Mean (%CV) Nevirapine Pharmacokinetic Parameters After Multiple Oral Administrations of Nevirapine 200 mg BID, Stavudine 40 mg BID and Nelfianvir 750 mg TID

	AUC	$C_{min,ss}$	$C_{max,ss}$	T_{max}	*CL/F*
	μg·hr/mL	*μg/mL*	*μg/mL*	*hours*	*L/hr*
Mean	64.3	4.57	6.73	3	3.32
%CV	26	35	22	38	26

Table 9. Mean (%CV) Nelfinavir Pharmacokinetic Parameters After Multiple Oral Doses of Nelfinavir 750 mg BID and Stavudine 40 mg BID Both With and Without Nevirapine 200 mg BID

	Without Nevirapine	*With Nevirapine*	*Difference*
AUC (*μg·hr/mL*)	19.7 (38)	19.05 (43)	-3%
$C_{max,ss}$ (*μg/mL*)	3.39 (31)	3.64 (37)	+7%
$C_{min,ss}$ (*μg/mL*)	2.16 (50)	1.95 (66)	-9%

Comments

1. This study was not designed to characterize the pharmacokinetic effect of nelfinavir on nevirapine. If the sponsor wishes to include language based on historical data, they will need to submit a more rigorous comparison to any existing information.

2. The sponsor is requested to submit representative [redacted] from the nevirapine assay to establish its specificity.
3. The sponsor is requested to provide individual and mean concentration versus time data for nevirapine and AG1402. Additionally, they are requested to submit mean and individual pharmacokinetic parameter estimates for AG1402 both with and without nevirapine.

Conclusion This trial was not designed to describe the effect of nelfinavir on nevirapine and did not include data to describe the effect of nevirapine on nelfinavir's major metabolite, AG1402. Therefore, even though the changes in nelfinavir bioavailability are consistently small when given with nelfinavir, as submitted, this study report does not support any labeling claims.

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Study DMP 266-019 (IND[redacted])
Study Title: A Phase I, Open-Label Study in Healthy Volunteers to Evaluate the Potential for a Pharmacokinetic Interaction Between DMP-266 and Viracept™ (Nelfinavir Mesylate)

The objective of this study was to evaluate the potential for a pharmacokinetic interaction between efavirenz and nelfinavir when the two drugs were coadministered. This study was conducted in healthy adults male and female volunteers. Twenty male subjects entered Cohort I (8 Caucasian, 8 Black, 4 Hispanic). Nineteen male subjects and one female subject entered Cohort II (7 Caucasian, 7 Black, 5 Hispanic, 1 Asian/ Pacific Islander).

Cohort I utilized a single period design. Subjects were randomized into two groups of 10 subjects.
Group 1:
Days 1-7: Nelfinavir 750 mg q8hr
(Day 7: 8 hr nelfinavir PK profile)
Days 8-14: Nelfinavir 750 mg q8hr plus efavirenz 400 mg qd
(Day 14: 8 hr nelfinavir PK profile; 24 hr efavirenz PK profile)
Group 2:
Days 1-7: Efavirenz 400 mg qd
(Day 7: 16 hr efavirenz PK profile)
Days 8-14: Efavirenz 400 mg qd plus nelfinavir 750 mg q8hr
(Day 14: 24 hr efavirenz PK profile; 8 hr nelfinavir PK profile)

For concomitant administration, the morning dose of nelfinavir was given concurrently with the daily dose of efavirenz. All morning doses (efavirenz, nelfinavir, or combination) were administered 30 minutes after breakfast. All afternoon and evening doses (nelfinavir only) were administered 30 minutes after a light snack.

Cohort II utilized a two-period crossover design. Subjects were randomized into four groups of five subjects. In Groups 1 and 3, the effects of efavirenz on nelfinavir pharmacokinetics were assessed. In Groups 2 and 4, the effects of nelfinavir on efavirenz pharmacokinetics were assessed. The doses for Cohort II were based on the results from Cohort I and were selected in an effort to achieve plasma concentrations during combination therapy similar to the plasma concentrations observed when each drug is given alone at its usual dose.

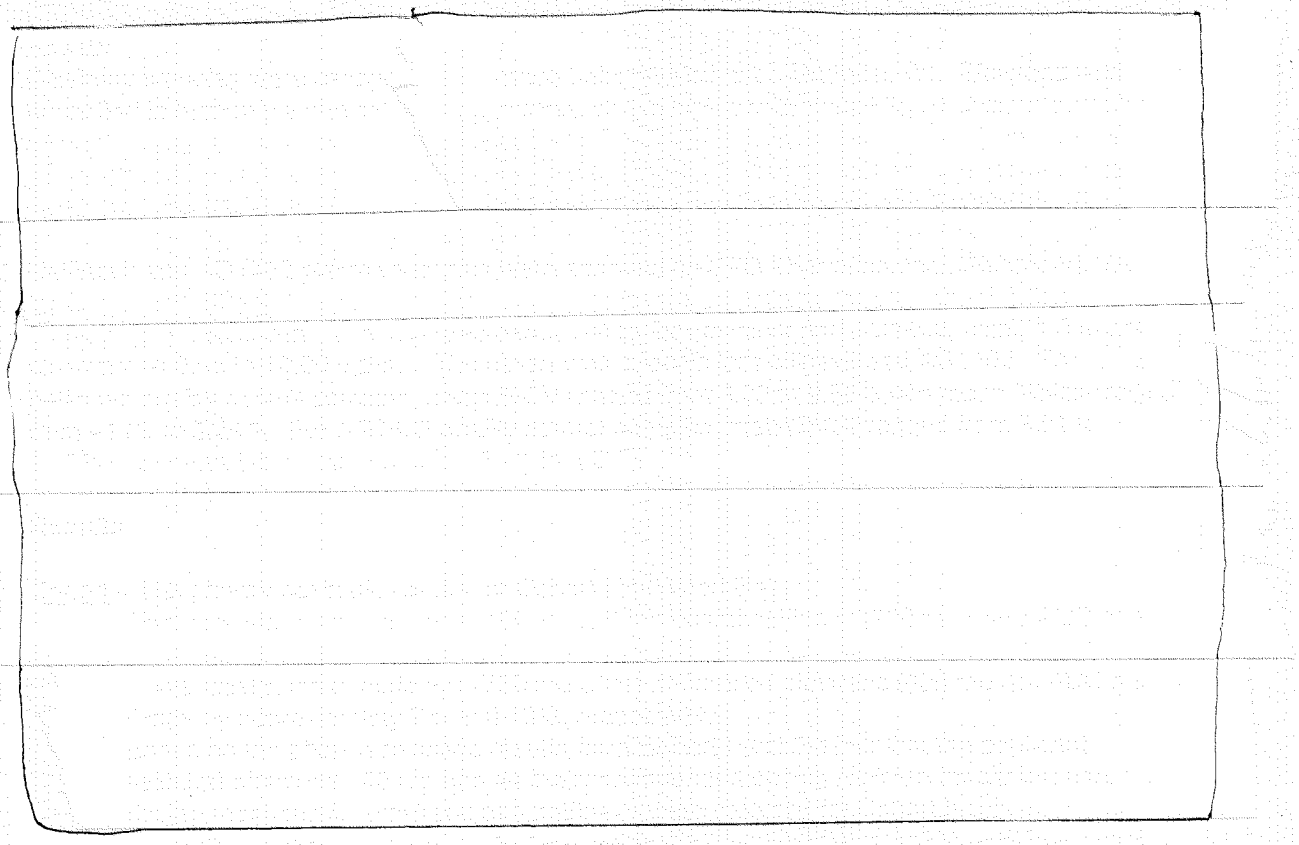
Group 1:
Period 1: Nelfinavir 750 mg q8hr for 7 days; 28 day washout
(Day 7: 8 hr nelfinavir and metabolite PK profile)
Period 2: Nelfinavir 750 mg q8hr + efavirenz 600 mg qhs for 7 days
(Day 7: 8 hr nelfinavir and metabolite PK profile; 24 hr efavirenz PK profile)
Group 2:
Period 1: Efavirenz 600 mg qhs for 7 days; 28 day washout
(Day 7: 24 hr efavirenz PK profile)
Period 2: Efavirenz 600 mg qhs + Nelfinavir 750 mg q8hr for 7 days
(Day 7: 24 hr efavirenz PK profile; 8hr nelfinavir and metabolite PK profile)
Group 3:
Period 1: Nelfinavir 750 mg q8hr + efavirenz 600 mg qhs for 7 days; 28 day washout
(Day 7: 8 hr nelfinavir and metabolite PK profile; 24 hr efavirenz PK profile)
Period 2: Nelfinavir 750 mg q8hr for 7 days
(Day 7: 8 hr nelfinavir and metabolite PK profile)
Group 4:
Period 1: Efavirenz 600 mg qhs + Nelfinavir 750 mg q8hr for 7 days; 28 day washout
(Day 7: 24 hr efavirenz PK profile; 8 hr nelfinavir PK profile)
Period 2: Efavirenz 600 mg qhs for 7 days

(Day 7: 24 hr efavirenz PK profile)

For concomitant administration, the evening dose of nelfinavir was given with the daily dose of efavirenz in Cohort II. All morning doses of nelfinavir were administered 30 minutes after breakfast. All afternoon doses of nelfinavir and bedtime doses of nelfinavir and efavirenz were administered 30 minutes after a light snack.

Pharmacokinetic parameters were determined using non-compartmental methods. In addition to efavirenz and nelfinavir, samples from Cohort II were assayed for AG1402, the active metabolite of nelfinavir. Statistical analyses were performed [redacted] Analysis of variance was performed using procedure GLM.

Formulations:
Efavirenz: 100 mg blue capsules; Lot 961644
Nelfinavir: 250 mg Viracept™ tablets



Cohort II:

Pharmacokinetic Parameters for Efavirenz 600 mg qhs (Cohort II, Groups 2 and 4, N=10)

	Arithmetic Mean ± SD		(Efavirenz + Nelfinavir)/Efavirenz	
Parameter	Efavirenz	Efavirenz + Nelfinavir	Geometric mean ratio	95% CI
AUCτ (μM*hr)	247.7 ± 77.7	228.7 ± 100.8	0.88	0.65, 1.18
Cmax (μM)	15.66 ± 3.04	14.29 ± 4.78	0.88	0.68, 1.13
Cmin (μM)	7.64 ± 2.91	7.28 ± 3.66	0.90	0.65, 1.25
Tmax (hr)	*3.5 (2.0 - 4.0)	*4.0 (2.0 - 6.0)	NA	NA

*median (range); NA=not applicable

There coadministration of nelfinavir did not cause a statistically significant change in any efavirenz pharmacokinetic parameters.

Pharmacokinetic Parameters for Nelfinavir 750 mg q8hr (Cohort II, Groups 1 and 3, N=7)

	Arithmetic Mean ± SD		(Nelfinavir + Efavirenz)/Nelfinavir	
Parameter	Nelfinavir	Nelfinavir + Efavirenz	Geometric mean ratio	95% CI
AUCτ (μg*hr/mL)	25.8 ± 10.0	30.3 ± 10.3	1.20	1.05, 1.38
Cmax (μg/mL)	4.30 ± 1.43	5.16 ± 1.63	1.21	1.08, 1.36
Tmax (hr)	*3.0 (2.0 - 3.0)	*3.0 (2.0 - 7.9)	NA	NA

*median (range); NA=not applicable

The coadministration of efavirenz caused a statistically significant increase in nelfinavir AUC and Cmax.

Pharmacokinetic Parameters for the Nelfinavir Metabolite, AG1402 (Cohort II. Groups 1 and 3, N=7)

	Arithmetic Mean ± SD		(Nelfinavir + Efavirenz)/Nelfinavir	
Parameter	Nelfinavir	Nelfinavir + Efavirenz	Geometric mean ratio	95% CI
AUCτ (μg*hr/mL)	7.83 ± 3.64	5.19 ± 2.74	0.63	0.50, 0.79
Cmax (μg/mL)	1.48 ± 0.69	0.92 ± 0.44	0.60	0.50, 0.73
Tmax (hr)	*3.0 (3.0 - 4.0)	*4.0 (3.0 - 6.0)	NA	NA

*median (range); NA=not applicable

The coadministration of efavirenz with nelfinavir caused a statistically significant decrease in AG1402 AUC and Cmax.

Discussion:

The results from this study indicate that efavirenz inhibits the metabolism of nelfinavir. In previous clinical studies, efavirenz induced the metabolism of indinavir, a CYP3A4 substrate. However, in vitro studies with efavirenz have shown it inhibits CYP3A4, CYP2C9, and CYP2C19 with Ki values of approximately 8.5 - 17 μM. Nelfinavir is metabolized by several cytochrome P450 enzymes: CYP3A4>2C19>2D6>2C9.

The results from this study suggest that coadministration nelfinavir may increase the clearance of efavirenz, although the changes in efavirenz pharmacokinetic parameters were not statistically significant. These non-significant changes may be due to enzyme induction. Nelfinavir is an inhibitor of CYP3A4. Nelfinavir also decreases the concentrations of zidovudine and ethinyl estradiol, which are metabolized by oxidation and/or glucuronidation. Efavirenz is metabolized in vitro to 8-hydroxy efavirenz by CYP3A4 and CYP2B6; in in vivo studies a glucuronide conjugate of 8-hydroxy efavirenz has been found in plasma and urine.

The effects of efavirenz and nelfinavir on one another's pharmacokinetics were similar when either 400 mg qd or 600 mg qhs efavirenz were coadministered with nelfinavir 750 mg q8hr.

Conclusion:

Nelfinavir at a dose of 750 mg q8hr did not alter the steady state AUCτ or Cmax of efavirenz at a dose of 600 mg qhs. Efavirenz at dose of 600 mg qhs increased nelfinavir AUCτ by approximately 20% and Cmax by approximately 21%. The results were similar when efavirenz 400 mg qd was administered with nelfinavir 750 mg q8hr.

The changes observed in this study were not clinically significant. Efavirenz and nelfinavir may be coadministered together without adjusting the dose of either drug.

/S/ 6/10/99

Bradley K. Gillespie, PharmD
Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation III

Concurrence: /S/ 6/10/99

Kellie Schoolar Reynolds, PharmD
Team Leader, Antiviral Drug Products Section

cc:

HFD-530	/NDA 20-779
	/MO/Wu
	/CSO/Lynche
HFD-880	/Gillespie
	/TL/Reynolds
	/DPE III
HFD-340	/Viswanathan
CDR	/Barbara Murphy

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Clinical Pharmacology and Biopharmaceutics Review Addendum

NDA 20-779 (SE8-022) Reviewer: Robert O. Kumi, Ph.D.
Drug: VIRACEPT (nelfinavir mesylate) Draft Review : 11/26/99
Company: Agouron Pharmaceuticals Inc.

I. Introduction

Supplement (SE8-022) to NDA 20-779 primarily provides clinical efficacy and safety data to support BID dosing of VIRACEPT. Additionally, data from a pharmacokinetic subset study and three drug interaction study reports are included in the submission. Subsequently, the sponsor submitted (September, 1999) labeling revisions to the current VIRACEPT package insert to incorporate this new information.

This supplemental NDA was reviewed by Dr. Bradley Gillespie in June, 1999 and this review is an addendum to Dr. Gillespie's review. The addendum outlines the content of the labeling changes suggested by the Agency in response to the sponsor's proposed label and the corresponding action of the sponsor. Revisions are in the form of deletions, additions and alternative wordings to the CLINICAL PHARMACOLOGY (Pharmacokinetics and Drug Interactions), WARNINGS, PRECAUTIONS (Information for Patients and Drug Interactions) and DOSAGE AND ADMINSTRATION sections of the VIRACEPT Package Insert. The last section of the addendum addresses some of Dr. Gillespie's comments from his review. It is noted that these comments were not forwarded to the sponsor, but the comments were discussed internally. The final approved version of the label will be included with this addendum.

II. Labeling Revisions

A. CLINICAL PHARMACOLOGY

1. Pharmacokinetics

Agency's Proposal

The sponsor was asked to provide additional information on the pharmacokinetic study results by indicating the number of studies conducted, dosing duration, time of trough determination and to consider including a statement on potential diurnal variation.

Sponsor's Action

The sponsor provided the requested information on the pharmacokinetic study results and indirectly addressed the possibility of diurnal variation.

2. Drug Interactions

Agency's Proposal

The sponsor was asked to remove information about the effect of nelfinavir on nevirapine pharmacokinetics (drug interaction table) as the study design was inappropriate to describe this interaction.

Sponsor's Action

The sponsor removed the drug interaction information as requested by the Agency.

B. WARNINGS

Agency's Proposal

The sponsor was asked to include information regarding the potential adverse reactions resulting from coadministration of nelfinavir and sildenafil.

Sponsor's Action

The sponsor agreed to the Agency's suggestion.